*Eur J Cancer Clin Oncol*, Vol. 21, No. 1, pp. 5–7, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00


## *Perspectives and Commentaries*

# Chemotherapy of Esophageal Cancer

D. KELSEN

*Memorial Sloan Kettering Cancer Center, Department of Medicine, Solid Tumor Service, New York, U.S.A.*

(A COMMENT ON: De Besi P, Salvagno L, Endrizzi L *et al.* Cisplatin, bleomycin and methotrexate in the treatment of advanced oesophageal cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 743–747.)

ESOPHAGEAL cancer remains a highly virulent disease with a poor prognosis. Long-term survival statistics have shown no significant improvement over the last 15–20 yr; currently only 5–10% of all patients will be alive 5 yr from their date of diagnosis [1]. The disease is endemic in China, South Africa, Iran and southern Russia, and has high incidence areas in the United States and in Europe. The conventional treatment for patients with loco-regional disease (tumor clinically limited to the esophagus and periesophageal tissues) is the use of surgery or radiation therapy. The results of this approach have recently been summarized [2, 3]. In essence, approximately 60% of patients present with potentially operable disease; 40% have resectable tumors. For radiation therapy, only 49% receive potentially curative doses (4500–5500 rad); the remaining patients are given palliative radiation. The survival data for both modalities was equally dismal: 18% of patients are alive at 1 yr and 4–6% at 5 yr.

Several autopsy studies have demonstrated that, in symptomatic patients (as opposed to those found during mass screening procedures), epidermoid carcinoma of the esophagus is probably widely disseminated even at diagnosis [4, 5]. Anderson and Lad [4] reviewed a series of 79 patients treated at the Chicago Veterans Administration Hospital. The median interval from diagnosis to death was 4 months, suggesting that the autopsy findings were not a result of a prolonged disease-free interval. Over 85% of patients had widespread tumor at post-mortem: liver, lung and lymph nodes were the most common sites. Simiarly, Attah and Hadju [5] reviewed the records of 113 autopsies performed at the Cleveland Metropolitan General Hospital: 73% of their patients had metastatic disease.

These studies suggest that in view of the systemic nature of the tumor, effective chemotherapy should, in theory at least, play a major role in the management of patients with esophageal cancer. There has, however, at least until recently, been little investigation in this area. In the last 5-8 yr the pace of study has increased, and there are now at least some data available on a number of single agents, as well as several combination regimens. The results of these trials have recently been summarized [6].

Ten drugs have had adequate trials in at least 19 patients each, so that some statement can be made regarding efficacy at the 15% level. For the earlier studies with agents such as bleomycin, patients with esophageal cancer were included in broad phase II trials. More recently, disease-oriented studies have been performed. Bleomycin, cisplatin, vindesine and mitomycin are the most well studied drugs. All have modest-to-moderate activity, in the 10–20% range.

For bleomycin the median duration of response as a single agent was only 1.5–2.5 months. Cisplatin and vindesine had somewhat longer median response durations (4–5 months). The response data for mitomycin is primarily based on a recently reported study from the ECOG, in which a high dose schedule was used [7]. Although the response rate in this small trial was substantial (42%), toxicity, primarily myelosuppression, was severe. The response rate using smaller, more well tolerated doses is probably lower, judging by earlier reports. The other agents have had more limited trials, and their 95%

Accepted 5 April 1984.

confidence limits are rather broad. With any of the single agents, complete remissions are very rare.

As indicated by the study of DeBesi *et al.* [12], combination regimens are now entering clinical trial. The rationale for their use, of course, is the higher response rates seen in a number of other neoplasms when multi-drug combinations are used. To date, approximately ten different esophageal cancer regimens have been reported, either in final or in abstract form. Cisplatin is the common denominator in almost all of these trials. Most series have involved less that 25 patients, so that the observed response rates must be interpreted cautiously. In addition, the criteria of response used must be considered. For patients with metastases to lungs, lymph nodes or subcutaneous tissue, it is fairly easy to evaluate response; the criteria of Miller *et al.* [8] are usually used. However, for patients in whom the primary esophageal tumor is either one of, or is the only site of disease, bidimensionally measurable parameters are clearly not present. A number of studies from Memorial Hospital have demonstrated that major changes in swallowing can be seen with minimal increases in the esophageal lumen. Thus, it is clear that subjective relief of dysphagia should not be employed in assessing drug or radiation effectiveness. Barium contrast studies can be used, with the understanding that they represent evaluable rather than measurable disease. In this setting rather stringent criteria for response are required; return of the barium swallow to normal does not mean a complete response. These patients should at the least undergo endoscopy. For those patients treated pre-operatively, a complete remission means, to us, that no viable tumor was found in any site sampled, including the esophageal specimens, lymph nodes and visceral organs [9]. Using these criteria (endoscopy and surgery) true complete remissions are still relatively rare.

Response rates with multi-drug regimens range from 15–25% for cisplatin–bleomycin to 33–80% for other platinum-containing combinations. The largest series of patients treated with chemotherapy are from Memorial Hospital, utilizing either cisplatin and a bleomycin infusion or the three-drug combination of cisplatin–vindesine–bleomycin (DVB). For the DVB combination the response rate, in a group of 68 evaluable patients, was 53%. For patients with extensive disease, treated primarily with chemotherapy alone, the median duration of response was 7 months [10].

DeBesi and colleagues have expanded on the initial studies of Vogel *et al.* with the three-drug combination of cisplatin, methotrexate and bleomycin. In a small group of ten patients Vogel had reported five responses [11]. In this larger series of 31 patients, DeBesi *et al.* noted that ten showed partial responses [12]. They point out that the performance status of their patients may have been poorer than those of Vogel *et al.*, leading to an observed response rate that was lower than that of the initial report. While it appears clear that, as is the case in other solid tumors (e.g. lung, colon, stomach), patients with a poor performance status are less likely to respond to chemotherapy, another explanation for their findings is that there actually is no difference between the two trials, whose 95% confidence limits overlap.

What does seem apparent from currentlu available data is that epidermoid carcinoma of the esophagus, while still a most difficult disease, is not totally refractory to chemotherapy. With moderate activity seen with several regimens, combined modality approaches for patients with loco-regional disease are now under study. Several preliminary trials, from a number of centers, indicate that pre-operative chemotherapy can be given safely, with no increase in operable morbidity or mortality. In the pilot trials at Memorial Hospital, for example, resection rates were 76 and 82% in the cisplatin–bleomycin and cisplatin–vindesine–bleomycin studies respectively. Operative mortality was 11 and 5.6%. For the more effective DVB combination the median duration of survival was 16.2 months, which appears to be significantly improved when compared to a historical control group receiving less effective cisplatin–bleomycin [10]. These preliminary studies are currently being further evaluated in prospective, controlled trials.

It should also be clear, however, that despite these encouraging early results, there are currently no comparative trials of single agent vs muti-drug combinations. Furthermore, the optimal drug regimen and schedule remains to be defined. Toxicities of currently used combinations are substantial, although usually tolerable. The dose limiting toxicity of the DVB, for example, was leukopenia. Extremely ill patients (Karnofsky performance status of less than 50) in our hands only occasionally respond to aggressive combination chemotherapy, and may have more severe toxicity. Thus the use of chemotherapy in this disease either as a single modality as palliation for advanced disease, or as part of a combined approach including surgery and/or radiation, should still be considered investigational. Randomized trials of pre-operative chemotherapy (with ot witout concomitant radiation), as well as new drug trials, should have a high priority.

## REFERENCES


1. Rosenberg JC, Schwade JG, Vaitkevicius VK. Cancer of the esophagus. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, PA, Lippincot, 1982, 499–533.
2. Earlham R, Cunha-Melo J. Oesophageal squamous cell carcinoma: I: A critical review of surgery. *Br J Surg* 1980, **67**, 381–390.
3. Earlham R, Cunha-Melo J. Oesophageal squamous cell carcinoma II: A critical review of radiotherapy. *Br J Surg* 1980, **67**, 457–461.
4. Anderson L, Lad T. Autopsy findings in squamous cell carcinoma of the esophagus. *Cancer* 1982, **50**, 1587–1590.
5. Attah E, Hadju S. Benign and malignant tumors of the esophagus at autopsy. *J Thorac Cardiovasc Surg* 1968, **55**, 396–404.
6. Kelsen D. Chemotherapy of esophageal cancer. *Semin Oncol* 1984, **11**, 159–168.
7. Engstrom PF, Lavin PT, Klaassen DJ. Phase II evaluation of mitomycin and cisplatin in advanced esophageal carcinoma. *Cancer Treat Rep* 1983, **67**, 713–715.
8. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting of cancer treatment. *Cancer* 1981, **47**, 207–214.
9. Kelsen DP, Heelan R, Coonley L *et al.* Clinical and pathological evaluation of response to chemotherapy in patients with esophageal carcinoma. *Am J Clin Oncol* 1983, **6**, 539–546.
10. Kelsen D, Hilaris B, Coonley C *et al.* Cisplatin, vindesine and bleomycin combination chemotherapy of local–regional and advanced esophageal cancer. *Am J Med* 1983, **75**, 654–652.
11. Vogel S. Effective chemotherapy for esophageal cancer with methotrexate, bleomycin and *cis*diamminedichloroplatinum (II). *Cancer* 1981, **48**, 2555–2558.
12. DeBesi P, Salvagno L, Endrizzi L *et al.* Cisplatin, bleomycin and methotrexate in the treatment of advanced oesophageal cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 743–747.